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OVERALL SUMMARY FOR FLUOROBENZENE

Summary

Fluorobenzene is a liquid with a water solubility of approximately 1540 mg/L. Fluorobenzene has a freezing point of -40ºC, boiling point of 84.73ºC at 760 mm Hg, density of 1.024 g/mL, and a vapor pressure of 100 mm Hg at 30.4ºC.

A review of estimated physical-chemical properties and environmental-fate characteristics indicates that fluorobenzene may be persistent in air with an estimated half-life due to hydroxyl radical oxidation of 23.3 days. Based on the BIOWIN ultimate survey model estimate of weeks-to-months, fluorobenzene may be moderately persistent in terrestrial compartments, and is not expected to readily biodegrade (Table 1). Fluorobenzene is not highly bioaccumulative with an estimated BCF of 11.17 (Table 1). When modeled using a Level III fugacity model under a standard scenario of equal emissions to air, water, and soil, fluorobenzene is expected to partition primarily into air and water compartments (Table 1). The Hydrowin model (v. 1.67, Syracuse Research Corporation) could not estimate a hydrolysis rate for fluorobenzene in regard to stability in water. However, halogenated aromatics/PCBs are generally resistant to hydrolysis (Harris, 1990), and thus fluorobenzene would be likely to be stable to hydrolysis in water. A hydrolysis test using OECD Guideline 111 is recommended to confirm this prediction.

Table 1 : Environmental Fate

Bioconcentration*	BCF = 11.17
Biodegradation*	Does not readily biodegrade
Fugacity*	Level III Partition Estimate Air 40.9 % Water 44 % Soil 14.8 % Sediment 0.245 %
* Modeled data	

In aquatic organisms, fluorobenzene has low toxicity with a 96-hour LC_{50} in fathead minnows of 210 mg/L. Fluorobenzene was moderately toxic to *Daphnia* in a 24-hour study which produced an EC_{50} of 7.37 mg/L. Modeling of physical-chemical parameters (i.e., log Kow) and aquatic toxicity was conducted to help provide insight into the behavior in the environment and the aquatic toxicity of fluorobenzene (See Table 2). Syracuse Research Corporation models for estimating physical-chemical properties were used to estimate $\log_{10}$ Kow (Meylan and Howard, 1995) for subsequent use in the ECOSAR program. ECOSAR (Meylan and Howard, 1999) was used to estimate aquatic toxicity data for green algae, daphnids (planktonic freshwater crustaceans), and fish. ECOSAR predictions are based on actual toxicity test data for classes of

compounds with similar modes of action. The predicted $\log_{10}$ Kow value was used as input for the ECOSAR model (see Table 2 for values). The ECOSAR predictions indicate that fluorobenzene is of low to medium concern relative to acute toxicity to algae, invertebrates, and fish.

Additional aquatic toxicity data are presented for another mono-substituted halobenzene (chlorobenzene) as well as several di-substituted halobenzenes (chloro-fluorobenzenes). The acute fish, daphnid, and algae data for chlorobenzene support the data presented for fluorobenzene. Although the fluorobenzene and chlorobenzene acute test data for daphnids are from 24-hour tests, the 48-hour chloro-fluorobenzene test data (based on measured test concentrations) support the data for the monosubstituted halobenzenes. Estimated toxicity data from ECOSAR agree reasonably well with experimental data except for invertebrates. ECOSAR appears to underestimate the toxicity of these compounds to daphnids, but the experimental data are adequate for acute hazard assessment. The existing data (experimental and estimated) are also adequate for assessing acute hazard to fish and algae, therefore no additional testing is necessary.

Table 2: Aquatic Toxicity Values

	Fluorobenzene	Chlorobenzene	1-Chloro-2-fluorobenzene	1-Chloro-3-fluorobenzene	1-Chloro-4-fluorobenzene
Log Kow	2.19	2.64	2.84	2.84	2.84
Toxicity to Fish (LC_{50} value)	96-hour: 210 mg/L (N) 48-hour: 430.5 mg/L (N) 96-hour: 47.2 mg/L (E)	96-hour: 10.4 mg/L (N) 96-hour: 20.9 mg/L (E)	No test data. 96-hour: 15.7 mg/L (E)	No test data. 96-hour: 15.7 mg/L (E)	No test data. 96-hour: 15.7 mg/L (E)
Toxicity to Invertebrates (EC_{50} value)	24-hour: 7.37 mg/L (M) 48-hour: 51.3 mg/L (E)	24-hour: 4.3 mg/L (N) 48-hour: 23.4 mg/L (E)	48-hour: 2.28 mg/L (M) 48-hour: 17.8 mg/L (E)	48-hour: 3.64 mg/L (M) 48-hour: 17.8 mg/L (E)	48-hour: 1.70 mg/L (M) 48-hour: 17.8 mg/L (E)
Toxicity to Algae (EC_{50} value)	No test data. 96-hour: 32.4 mg/L (E)	96-hour: 12.5 mg/L (N) 96-hour: 15.2 mg/L (E)	No test data. 96-hour: 11.7 mg/L (E)	No test data. 96-hour: 11.7 mg/L (E)	No test data. 96-hour: 11.7 mg/L (E)
E = estimated value, N = value based on nominal test concentrations. M = value based on measured test concentrations.					

Fluorobenzene has very low acute oral toxicity with an acute lethal dose (ALD) > 11,000 mg/kg in rats and an LD_{50} in rats of 4399 – 9500 mg/kg. No clinical signs of toxicity were observed in

the non-lethal doses; however, slight to severe weight loss was noted. Fluorobenzene also had very low acute inhalation toxicity with a 4-hour acute lethal concentration (ALC) of 6200 ppm in rats and an LC_{50} in rats of 6835 ppm. When applied to the skin of rabbits, fluorobenzene produced no to mild erythema and no to severe edema and was considered a mild skin irritant. Fluorobenzene did not induce dermal sensitization in guinea pigs. Fluorobenzene was moderately irritating to the rabbit eye in one study, and severely irritating in two other studies containing limited information. More severe effects were observed in eyes that were washed than those that remained unwashed.

In a 28-day repeated dose study, groups of rats were exposed nose-only, 6 hours a day to 0.37 mg/L (94 ppm), 1.50 mg/L (381 ppm), or 6.24 mg/L (1585 ppm) of fluorobenzene. Slight changes in physical condition were seen for rats exposed to 1.50 or 6.24 mg/L. Other effects of treatment were confined to adaptive liver changes and unique male rat hydrocarbon nephropathy. Although the adaptive liver changes extended into the low dose group (0.37 mg/L), neither of these conditions were considered to be indicative of toxicologically important adverse effects of treatment and, consequently, the NOAEL was considered to be 0.37 mg/L (94 ppm). Furthermore, the slight changes observed in physical condition were not indicative of serious damage to the health of the animals. There was, however, evidence of a treatment-related increase in fluoride concentration in bones and teeth of animals from all exposure groups.

No data on potential developmental toxicity of fluorobenzene were available. However, several developmental toxicity studies have been conducted using the close structural analogue chlorobenzene. These compounds have similar log Kow values (2.19 and 2.64 for fluoro- and chlorobenzene, respectively), suggesting that maternal/fetal partitioning for these compounds is likely to be similar. Fluoro- and chlorobenzene are also metabolized by similar pathways, with *para*- and *ortho*-phenols as the major products (Koerts et al., 1997; Rietjens et al., 1993). Phenolic metabolites of both compounds are subsequently conjugated with glucuronic acid and excreted. These similarities suggest that chlorobenzene should serve as a suitable model for fluorobenzene with regard to prediction of developmental toxicity. This conclusion is supported by *in silico* analysis of fluoro- and chlorobenzene using TOPKAT (Health Designs Inc, Rochester, NY) and MultiCASE (MULTICASE Inc., Cleveland OH). TOPKAT predicted both compounds to be negative for developmental toxicity in mammals. Similarly, MultiCASE predictions using modules for rabbit, rat, and mouse teratogenicity were negative for both halobenzenes.

The developmental toxicity studies for chlorobenzene indicated that chlorobenzene was not a unique developmental toxin in either rats or rabbits. Pregnant female Fisher-344 rats were exposed to 0, 75, 210, or 590 ppm chlorobenzene in air for 6 hours/day on days 6-15 of gestation. The maternal NOAEL was 210 ppm. Maternal toxicity occurred at 590 ppm as evidenced by decreased body weight gain on gestation days 6-8 and increased absolute and relative liver weights at study termination on gestation day 21. The fetal NOAEL was also 210 ppm based on an increase in skeletal variations (delayed ossification of vertebrae centra and bilobed thoracic centra) at 590 ppm. These variations were indicative of a slight delay in skeletal development among the fetuses (mild fetotoxicity) at a maternally toxic dose. The incidence of malformations (collectively or individually) was not increased in any of the exposed groups.

In addition, two inhalation developmental studies on chlorobenzene were conducted in rabbits. Pregnant female New Zealand white rabbits were exposed to 0, 75, 210, or 590 ppm chlorobenzene in air (first study) or 0, 10, 30, 75 or 590 ppm chlorobenzene in air (second study) for 6 hours/day on days 6-18 of gestation. The maternal NOAEL was 75 ppm based on significantly increased absolute and relative liver weight at 210 and 590 ppm at study termination on gestation day 29. In the first study, a few chlorobenzene-exposed fetuses exhibited visceral malformations which were not observed among concurrent controls. However, there was no dose-related increase in malformations and there was no increase in malformations in chlorobenzene-exposed groups in the subsequent study. In the second study there was a significant increase in litters with resorptions at 590 ppm, although this effect was not observed at any concentration on the first study, and was within the range of historical controls. Therefore the conclusion was that chlorobenzene did not have an embryotoxic effect on rabbits.

Fluorobenzene was not mutagenic in the Ames test. Fluorobenzene was tested in a second preincubation assay in *Salmonella* strains TA100, TA1535, and TA98, without metabolic activation and with rat and hamster liver activation; a positive result with hamster liver activation was observed in strains TA100 and TA1535. More weight was placed on the second study because a wider range of doses was tested and the chemical was tested up to the highest dose permitted by toxicity. Fluorobenzene was not clastogenic in a mouse bone marrow micronucleus test.

Test plan: A hydrolysis test using OECD Guideline 111 is recommended. As described below, the test material is a closed system intermediate; therefore, repeated dose and reproductive toxicity endpoints are not required.

Human Exposure Information

Fluorobenzene is received at a contract manufacturing site in isotanks that are delivered from ocean freight ports of entry into the U.S. It is pumped directly from the isotank into steel tanks in a diked area prior to use in production. This is a closed system. It is then pumped from the storage tank into the reactors for processing. This is also a closed system. At the end of the processing, the fluorobenzene has been consumed. During the purification of the product(s), any residual fluorobenzene is recovered to closed drums and then recycled into the process. Fluorobenzene has some vapor pressure, and so fugitive fluorobenzene vapors from the process are captured by an aqueous scrubber. That fluorobenzene is recovered and recycled. All hoses, lines, and fittings are inspected prior to use, and drained and dried after use.

During these operations, operators wear appropriate personal protective equipment (PPE) to protect themselves from splash and vapor. All waste and byproduct liquids (including water) that might contain fluorobenzene are captured and disposed of at regulated, off-site treatment, storage, and disposal facilities (TSDF's) or publicly owned treatment works (POTW's).

Potential exposure may occur during unloading and processing when operators are measuring the volumes in the tanks and process equipment. There is also the potential for exposure when any recovered fluorobenzene is drummed and transferred into the tank after recovery. At these times

operators wear appropriate PPE. There is also the potential for exposure to fugitive emissions during line breaking operations or in the event of equipment failure. Operators and maintenance personnel wear appropriate PPE during line-breaking and maintenance operations to protect themselves from splash and vapor.

PPE consists at a minimum of safety glasses with side shields, goggles (or face shield), gloves, coveralls, workboots, and respirators with organic vapor/acid gas cartridges. Additional PPE may also be required, depending upon other issues relevant to the operation being carried out. Safety showers, eyewash stations, and Self Contained Breathing Apparatus (SCBA) are available in close proximity to the operations area.

The contract manufacturer has procedures, practices, and controls in place to manage the risk of exposure and no incidents have been reported to DuPont. DuPont practices Responsible Care® and assesses the ability of a potential contract manufacturer to safely handle fluorobenzene prior to commencing a commercial relationship. This assessment includes reviews and audits of PPE, safety equipment and procedures, structural integrity, and safety practices.

The DuPont Acceptable Exposure Limit (AEL) for fluorobenzene is 25 ppm (8- and 12-hour TWA). No other limits have been established. Air monitoring has been conducted on fluorobenzene and results are shown in the table below.

EXPOSURE DATA

No. of Results	Exposure period TWA (ppm)	8-hour TWA (ppm)	Min. of Results (ppm)	Max of Results (ppm)
19	0.69	0.69	0.1	5.9

References for Summary:

Harris, Judith C. (1990). Rate of Hydrolysis, Ch. 7, Table 7-1, In Lyman, W.J. et al. (1990). Handbook of Chemical Property Estimation Methods, ACS, Washington, DC.

Koerts, J. et al. (1997). Chem. Res. Toxicol., 10(3):279.

Rietjens, I. M. C. M. et al. (1993). Biochemistry, 32(18):4801.

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Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).

TEST PLAN FOR FLUOROBENZENE

Fluorobenzene **CAS No. 462-06-6**	**Data Available**	**Data Acceptable**	**Testing Required**
Study	**Y/N**	**Y/N**	**Y/N**
PHYSICAL/CHEMICAL CHARACTERISTICS			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
ENVIRONMENTAL FATE			
Photodegradation	Y	Y	N
Stability in Water	N	N	Y
Transport (Fugacity)	Y	Y	N
Biodegradation	Y	Y	N
ECOTOXICITY			
Acute Toxicity to Fish	Y	Y	N
Acute Toxicity to Invertebrates	Y*	Y	N
Acute Toxicity to Aquatic Plants	Y**	Y	N
MAMMALIAN TOXICITY			
Acute Toxicity	Y	Y	N
Repeated Dose Toxicity	Y but NA	Y	NA
Developmental Toxicity	Y**	Y	N
Reproductive Toxicity	NA	NA	NA
Genetic Toxicity Gene Mutations (in bacterial cells)	Y	Y	N
Genetic Toxicity Chromosomal Aberrations (in *in vivo* micronucleus test)	Y	Y	N

* 24-hour data were available for the test chemical and 48-hour data were available for an analog chemical.
** Data were available on an analog chemical.

NA = not applicable